Atty. Docket No. 4512/80212

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Pharma Mar, S.A., et al.

SERIAL NO.: 09/787,461 (PCT/GB00/01857; designating the U.S.)

FILED: 15 May 2000 Group Art Unit: 3644

FOR: COMPOSITIONS AND USES OF ET-743 FOR TREATING CANCER

BOX DAC
ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, DC 20231

Sir or Madam:

SECOND DECLARATION OF ATTORNEY GRAHAM K. RUFFLES

In support of the Applicant's request for reconsideration of the denial of Applicant's petition for a retroactive foreign filing license, this declaration is made by European Patent Attorney Graham K. Ruffles, partner with Marks & Clerk of 57-60 Lincoln's Inn Fields, London WC2A 3LS, United Kingdom.

I. INTRODUCTION

1. This declaration relates to the following patent applications:

GB 9911183.3 filed 13 May 1999
GB 9911346.6 filed 14 May 1999
GB 9918534.0 filed 05 August 1999
GB 9927005.0 filed 15 November 1999
GB 9927106.6 filed 16 November 1999
GB 0007637.2 filed 29 March 2000; and

PCT/GB 00/01857, a PCT patent application designating the United States, filed in the United Kingdom Patent Office on Monday, 15 May 2000, claiming priority from the six UK patent applications noted above;

NON-PCT Filings based upon the six UK patent applications;

Argentina Application No. P000102321, filed 15 May 2000;

Chile Application No. 2000-1216, filed 15 May 2000; and

Malaysia Application No. PI 20002107, filed 13 May 2000.

2. The undersigned hereby declares that the subject matter of all of the above-mentioned patent applications was not under a secrecy order at the time of filing, and is not currently under any secrecy order.

3. I have represented Pharma Mar in their patent matters since the company was formed about 15 years ago. Pharma Mar is a pharmaceutical company with its headquarters and main offices in Madrid, Spain. Pharma Mar is now Spain's principal biopharmaceutical company, and a world leader in research and development of anti-tumour compounds from marine organisms. It is my understanding that the majority of Pharma Mar's research and development relating to its pharmaceutical products undergoing development is conducted in Spain at its headquarter facilities. For the reasons shown below, based on my past experience with Pharma Mar, and the information and documents given to me by Pharma Mar in connection with preparing and filing various priority applications, I had no reason to believe that any inventive work

relating to the six (6) above-identified priority applications occurred in the United States. Furthermore, upon my being informed of the names of the applicants of international application PCT/GB00/01857, and the residence in the United States of two of the applicants, I diligently began to investigate whether a U.S. foreign filing license was necessary for the earlier filed GB applications, the international PCT application, and the non-PCT national filings.

II. APPLICANT REASONABLY BELIEVED THAT NONE OF THE INVENTIVE SUBJECT MATTER OF THE GB APPLICATIONS HAD BEEN MADE IN THE UNITED STATES AT THE TIME OF FILING EACH OF THE GB PRIORITY DOCUMENTS

A. GB 9911183.3 FILED 13 MAY 1999.

1. GB 9911183.3 (Exhibit 1) describes a method of treating any mammal affected by a sarcoma or mesothelioma through the administration of ecteinascidin-743 (ET-743). Specifically, the invention relates to the use of antitumor compounds.

2. On 10 May 1999, I reviewed a letter dated May 7, 1999 from Pharma Mar instructing me to review various abstracts relating to the use of ET-743 to treat human sarcomas and mesotheliomas and to prepare and file a patent application relating to this subject matter. Because one of the abstracts was to be presented on 16 May 1999, I was asked to file the application, if possible, before 15 May 1999. PharmarMar's letter did not indicate that any part of this invention was made in the United States or that any inventor worked on this invention in the United States. Thus,

Pharma Mar did not provide me with any information that would have led me to believe that any of the work described in its letter had been conducted in the United States.

3. Pharma Mar forwarded the following four abstracts to me with its 7 May 1999 letter: (1) "Ecteinascidin (ET-743) in Heavily Pretreated Refractory Sarcomas: Preliminary Evidence of Activity;" (2) "Phase I and Pharmacokinetic Trial of Ecteinascidin-743 Administered as a 72 Hour Continuous Infusion;" (3) "Final Results of a Phase I Study of Ecteinascidin-743 24 Hours Continuous Infusion In Advanced Solid Tumors Patients;" and (4) "Ecteinascidin-743 24 Hours Continuous Infusion: Clinical and Pharmacokinetic Phase I Study Progressive Report." (Exhibit 2). Only the first abstract (I) was used to form part of the text of the application since I determined that the remaining 3 abstracts had probably already been published. In particular, the letter from Pharma Mar told me that abstracts (2) and (3) were already on the internet, and abstract (4) had been presented at a conference in November 1998. As the lead author on abstract (1) is listed with an address in France, and the abstract itself only identifies France and Spain as the various authors' countries of origin, there was no basis to believe that any of the work reported in the abstract was conducted in the United States.

Accordingly, based upon Pharma Mar's letter and the abstract, I had no reason to believe that any part of this invention was made in the United States.

I drafted the application on the basis of the work in abstract (1), to the effect that it had been discovered that ecteinascidin 743 had exceptional activity in the treatment of sarcomas and mesotheliomas. Sarcomas were the subject of abstract (1), and mesotheliomas were mentioned in the letter from Pharma Mar.

B. GB 9911346.6 FILED 14 MAY 1999.

1. GB 9911346.6 (Exhibit 3) is the same as GB 9911183.3 with the addition of a revised example.

2. Pharma Mar sent me a further revision of the example appearing in GB 911183.3 by facsimile late in the evening of 13 May 1999, after the filing of GB 9911183.3. In its facsimile, Pharma Mar provided some additional information on the sarcoma patients treated with ET-743. Nothing in this facsimile suggested that any of this work was being performed in the United States. One day later, on 14 May 1999, I filed GB 9911346.6 with the revised example.

3. Based upon the facsimile sent by Pharma Mar and the similarity of the subject matter to that of the prior GB 9911183.3 filing, I still had no reason to believe that any part of the invention was made in the United States.

C. GB 9918534.0 FILED 05 AUGUST 1999.

1. The text of GB 9918534.0 (Exhibit 4) as filed is the same as that of GB 9911183.3 and GB 9911346.6, except for references to other abstracts which further relate to the use of ET-743 to treat certain cancers and which describe possible mechanisms of action of ET-743.

2. On 29 July 1999, Pharma Mar provided another series of abstracts to me entitled (1) "A Phase I and Pharmacokinetic Study of ET-743 Evaluating a 3 Hours Intravenous Infusion In Patients With Solid Tumors;" (2) "In Vitro Effect of the Tetrahydroisoquinoline Alkaloid – Ecteinascidin-743 on Chondrosarcoma Cells;" (3) "Mode of Action of Ecteinasceidin-743;" (4) "Interference of Transcriptional Activation by

the Anti-Neoplastic Drug ET-743;" (5) "Changes in Gene Expression in Tumor Cells Exposed to the Two Marine Compounds Aplidine or ET-743 and Aplidine by Using c-DNA Microarrays;" (6) "Potent Antitumor Activity of ET-743 Against Human Soft Tissue Sarcoma Cell Lines;" and (7) "Importance of DNA Repair Mechanisms for the Sensitivity to ET-743." (Exhibit 5).

3. Abstracts (1) and (3) did not identify any authors as being from the United States; abstract (2) identified Hornicek, Francis J.; Weissbach, Lawrence; Nielsen, G Petur; Fondren, Gertrude; Harmon, David; Jimeno, Jose; Chabner, Bruce A.; and Faircloth, Glynn T of Massachusetts General Hospital and Pharma Mar USA, Inc., Cambridge, Massachusetts as authors; abstracts (4), (5) and (7) identified Faircloth, Glynn T of Pharma Mar USA, Inc as an author among respective European authors; and abstract (6) identified Weiwei Li, Jhanwar Suresh, Elisseyeff Yaroslav, and Joseph R. Bertino of Memorial Sloan-Kettering Cancer Center, New York, NY as authors. However, because the additional abstracts also relate to the use of ET-743 as a cancer chermotherapeutic, or to its possible mechanism of action as a cancer chemotherapeutic, I had no reason to believe at the time that there was any change in where the invention was made. In particular, abstract (2) related to *in vitro* work; abstracts (4), (5) and (7) related to mechanism of action; and abstract (6) related to activity against sarcoma cell lines and seemed merely to confirm the contents of the first GB filing.

4. As set forth in Section II above, it was my further understanding at the time I filed this application that all Pharma Mar research and protocols relating to the

project originated from Spain. I had no reason to believe anything different with respect to this application nor to believe that any of the inventive work was performed in the United States.

5. Based upon the conversation with Pharma Mar on July 29, 1999 and the abstracts provided to me on that date, I did not believe that any part of the invention was made in the United States or that a United States foreign filing license was necessary.

D. GB 9927005.0 FILED 15 NOVEMBER 1999.

1. GB 9927005.0 (Exhibit 6) contains the same information as the previously filed applications and was further modified to include an example relating to the results of a combination of ET-743 and dexamethasone in rats.

2. I prepared and filed GB 9927005.0 in response to a 15 November 1999 letter from Pharma Mar providing the data and information to be incorporated requesting an urgent filing in view of a planned disclosure of the data at a symposium the following day. Accordingly, the application was drafted and filed on 15 November 1999.

3. Based upon Pharma Mar's letter of 15 November 1999, and my knowledge of the facts surrounding the previous priority filing, I had no reason to believe that any of the additional information provided to me by Pharma Mar was made in the United States.

E. GB 9927106.6 FILED 16 NOVEMBER 1999.

1. GB 9927106.6 (Exhibit 7), filed 16 November 1999 contains information provided to me in the form of two additional abstracts.

2. Pharma Mar initiated the activity leading to the filing of GB 9927106.6 with another letter on 15 November 1999, the same day as the filing of GB 9927106.6. In the second letter, Pharma Mar requested an urgent filing in view of a symposium during which the following two abstracts were to be presented: (1) "Ecteinascidin-743 in Heavily Pretreated Refractory Sarcomas: Early Results of the French Experience" and (2) "Exploratory Evaluation of the Potential Predictors for Dose-Limiting Toxicities in Patients Treated With Ecteinasceidin-743 as a 24 Hour Intravenous Infusion Every 3 Weeks and Its Relationship to Pharmacokinetics."

3. Neither Pharma Mar's letter, nor the abstracts which only identified France, the Netherlands, and Spain as the countries of the authors, suggested or indicated to me that any of the additional work disclosed in the application was performed in the United States.

4. Accordingly, based upon the second Pharma Mar letter of 15 November 1999 and the abstracts enclosed therein, I had no reason to believe at the time that any part of the invention disclosed in the applications was made in the United States. Furthermore, due to the need to file urgently because of the imminent disclosure, I had no time to conduct any investigation to even raise the possibility of a United States involvement with the disclosed work.

F. GB 0007637.2 FILED 29 MARCH 2000.

1. GB 0007637.2 (Exhibit 8) filed 29 March 2000, is based on the earlier filed applications but incorporates information reported in additional abstracts provided to me by Pharma Mar, I believe, on 22 March 2000 during a visit to Spain.

2. Pharma Mar initiated discussions on the subject matter related to GB 0007637.2 during a meeting in Spain on 22 March 2000. The following abstracts formed part of the filed application: 1) "Characterization of 1Grov-1 Human Ovarian Cancer Cell Lines Made Resistant to Ecteinascidin-743;" 2) "Identification of Biochemical Parameters That Predict the Onset of Severe Toxicities in Patients Treated With ET-743;" 3) "Phase II Study of ET-743 in Advanced Soft Tissue Sarcoma in Adult;" 4) "Ecteinascidin Shows Promising Activity in Distinct Populations of Sarcoma Patients; Summary of 3 U.S. –Based Phase II Trials;" 5) "Ecteinascidin-743 in Taxane T/Anthracycline Pretreated Advanced/Metastatic Breast Cancer Patients: Preliminary Results With the 24 Hour Continuous Infusion 3 Week Schedule" and 6) "Preliminary Evidence of Activity of Ecteinascidin-743 in Heavily Pretreated Sarcomas of Bone and Soft Tissue Patients."

3. I acknowledge that G. T. Faircloth of Pharma Mar USA, Inc., Cambridge, Massachusetts is named as an author among other authors from Spain on abstract (1) and that G.D. Demetri, M. Seiden, R. Garcia-Carbonero, J. Supko, D. Harmon, G. Goss, P. Merriam, A. Waxman, M.T. Quigley, J. Jimeno, and D. Ryan of Dana-Farber Cancer Institute and Massachusetts General Hospital are listed as authors on abstract (4). However, due to the similarity of the subject matter to that of the

previous filings, i.e., relating to clinical aspects of ET-743 or its mechanism of action, I did not believe that there was any change of the material disclosed in the applications which had a significant enough basis in the United States to require a United States foreign filing license. In particular, abstract (1) relates to cell lines which are resistant to ecteinascidin 743, whereas my view was and is that any inventive activity resides in the use of ecteinascidin 743 against cells which are not resistant; and the abstract (4) on my cursory examination appeared to be merely confirmatory of the work in abstract (1) of the first GB filing, demonstrating activity against sarcomas.

4. Regarding the few abstracts which identify one or more United States authors, I did not believe that incorporating such material into a UK Priority application required a United States foreign filing license because the information reported in the abstracts generally related to information already disclosed in the first filed UK application which I believed to have been made outside of the United States.

G. BASED ON THE INFORMATION PROVIDED TO ME BY PHARMA MAR AND IN THE ABSTRACTS, I DID NOT BELIEVE THAT ANY OF THE GB PRIORITY APPLICATIONS DISCLOSED AN INVENTION REQUIRING A US FOREIGN FILING LICENSE

None of the six aforementioned UK priority filing applications list any inventors, or contain any claims, as is usual for a priority filing under UK practice. As set forth in Section II above, I had no reason to believe that the subject matter disclosed in the prior filings was either made in the United States or was of the nature requiring a foreign filing license based on my prior experience with Pharma Mar and the specific information received from Pharma Mar in connection with each of the Great Britain priority documents. (Exhibits 2-8). The priority filings relate mainly to the discovery of

beneficial effects in treating patients with sarcomas using ecteinascidin 743. That discovery appeared to be the subject of the first abstract of the first GB filing, which had authors based in Europe.

III. APPLICANT DILIGENTLY INVESTIGATED AND FILED A PETITION FOR A RETROACTIVE FOREIGN FILING LICENSE ONCE APPLICANT LEARNED THAT AT LEAST ONE OF THE INVENTIONS DISCLOSED IN THE GB PRIORITY APPLICATIONS MAY HAVE BEEN MADE IN THE UNITED STATES

1. On 15 May 2000, I filed international application PCT/GB00/01857, designating the United States as well as other countries, and claiming priority to the earlier filed GB applications. Three other non-PCT national applications were also filed on or about 15 May 2000. It was in connection with preparing the PCT filing that Pharma Mar identified the individuals Pharma Mar then believed may have made a contribution to the inventions. The other national non-PCT applications contain essentially the same PCT subject matter as the PCT application.

2. George D. Demetri and Daniel D. Van Hoff, both residents of the United States, are both named applicants of Pharma Mar's international application PCT/GB00/01857 (Exhibit 9) which designates the United States. It was only on 13 May 2001, upon receiving the inventorship details for the PCT application from Pharma Mar, that I first became aware that the PCT application, and possibly one or more of the earlier filed GB prior art applications, may contain subject matter requiring a United States foreign filing license. There was considerable extra disclosure in the PCT application, and I did not know the extent to which the inventors had been involved with the results described in the PCT and GB filings.

3. Upon receiving this information about the existence of individuals with an address in the USA, I immediately began an investigation to determine the location of the applicants at the time the invention disclosed in the PCT application was made and to determine whether any part of the invention may have been made in the United States. During the course of this investigation, I learned that two of the applicants of the PCT application, George D. Demetri and Daniel D. Van Hoff, were United States citizens at the time the invention was made, and that their contribution was made in the United States.

4. Upon being informed that two of the applicants were United States citizens, I immediately began to investigate whether it would be necessary to petition for a retroactive foreign filing license in the United States.

5. I, therefore, contacted Pharma Mar's U.S. counsel, Ernest Linek, on 4 July 2000, and asked him to prepare the necessary documents to obtain a retroactive foreign filing license in the United States. I continued to communicate and discuss the foreign filing license issue with him and to review and prepare a declaration outlining the facts underlying my filing of the six GB priority filing applications.

6. In February, 2001 I reviewed the document, signed it, and submitted it to Mr. Linek for filing in the USPTO.

7. It is my understanding that Mr. Linek timely filed a petition for a Retroactive Foreign Filing License on 2 March 2001.

IV. APPLICANT'S REQUEST FOR A RETROACTIVE FOREIGN FILING LICENSE SHOULD BE GRANTED.

1. Mr. Linek informed me that our petition for a Retroactive Foreign Filing License from the USPTO was denied on 1 March 2002.

2. It is my understanding that the Examiner denied our petition because 1) the petition did not contain a factual explanation underlying our contention that the material was erroneously filed in Great Britain without obtaining a foreign filing license, and 2) a showing that the license has been diligently sought after discovery of the proscribed foreign filing.

3. My Declaration In Support of Pharma Mar's request for reconsideration of the denial of Applicant's request for a Retroactive Foreign Filing License addresses each of the Examiner's concerns surrounding the filing of each of the Great Britain priority documents. Specifically, my declaration sets forth in detail the facts surrounding why I did not consider the need to obtain a foreign filing license before filing each of the priority documents in Great Britain.

In addition, once the potential error was discovered, I diligently investigated the facts surrounding where the invention may have been made and promptly caused to be filed a Request For A Retroactive Foreign Filing License as soon as I believed we had enough information to do so. The specific chronology of our efforts is set forth in section II above.

4. We respectfully submit that this Supplemental Declaration resolves the issues cited by the Examiner in her denial of our Petition For A Retroactive Foreign Filing License.

5. The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Graham K. Ruffles
Partner
Marks & Clerk

Date: 27 September 2002